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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/698,597	10/31/2003	Leonard G. Presta	39766-0033CP2C2-C1	1656

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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/698,597	PRESTA ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-11* is/are pending in the application.

4a) Of the above claim(s) *10 and 11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 6-9, a method for detecting a pathological condition, which is malignancy, comprising detecting the over-or under-expression of the ligand NT-4/5 (SEQ ID NO:45), using as a probe its receptor, SEQ ID NO:2, the truncated form thereof, SEQ ID NO:4, or an immunoadhesin thereof, are examined in the instant application.

The embodiment of claims 6-9, as drawn to a method of diagnosis of a pathological condition other than malignancy, using SEQ ID NO:45, or a method for detecting a pathological condition, including malignancy, by detecting the expression of BDNF (SEQ ID NO:42), NT-3 (SEQ ID NO:43) and NT-4 (SEQ ID NO:44), have been withdrawn from consideration as being drawn to non-elected invention. Claims 10-11 have been withdrawn from consideration as being drawn to non-elected invention.

Withdrawn Rejection

Rejection under 112, second paragraph, in view of the amendment.

Restriction

It is noted that the restriction requirement of the previous Office action has been made FINAL.

Claim Rejections - 35 USC § 112, First Paragraph, Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-9 remain rejected under 112, first paragraph, for lack of enablement for a method for diagnosis of malignancy, for reasons already of record in paper of 09/21/07.

1) The nature of the invention

The response asserts that the nature of the claimed invention is routine in the art, requiring routine steps of contacting and detecting over- or under-expression of a neurotrophic factor. The response asserts that moreover, the specification clearly names the particular pathological conditions to be diagnosed (see, e.g., page 91, lines 9-13), and discloses that these named pathological conditions may be diagnosed by the detection of over- or underexpression of a neurotrophin by detecting binding to a trk receptor (page 10, lines 20-25), such as a human trkB polypeptide (page 6, lines 7-32), and that the neurotrophin may be selected from BDNF, NT-3, NT-4, and NT-4/5 (page 16, lines 1-2).

The response has been considered but is not found to be persuasive for the following reasons:

Contrary to the assertion, the claimed method is not routine, encompassing a method for diagnosing a **genus** of numerous cancers, or tumors including abnormal growths, that over- or underexpresses a neurotrophic factor NT-4/5 (SEQ ID NO:45), using the **trkB receptor** SEQ ID NO:2 or SEQ ID NO:4 as a detecting **probe**, which probe however is **not specific for SEQ ID NO:45**. Further, not only the trkB receptor is not a specific probe, the **target** neurotrophic factor NT-4/5 (SEQ ID NO:45) is **not specific for the trkB receptor** SEQ ID NO:2 or SEQ ID NO:4, because SEQ ID NO:45 also binds to another receptor, the TrkA receptor. Although the

specification on page 91, line 11, recites a generic language "various types of tumors", the specification does not disclose, nor having objective evidence showing a particular cancer or particular tumor overexpressing SEQ ID NO:45, or a particular cancer or particular tumor underexpressing SEQ ID NO:45. The level of expression of a protein in a particular disease, including a particular cancer, however, is not predictable, in view of the teaching of Soontornniyooomkij et al and Guate et al, all of record. Further, whether one can use the trkB receptor SEQ ID NO:2 or SEQ ID NO:4 as a probe to detect SEQ ID NO:45 is unpredictable, because said probe is not specific for SEQ ID NO:45.

2) The state of the prior art.

The response asserts that Schneider et al., demonstrates that one can detect a malignancy, such as pancreatic cancer, by detecting the underexpression of NT-4. The response concludes that thus, the state of the prior art is supportive of enablement of the present invention.

The response has been considered but is not found to be persuasive for the following reasons:

Schneider et al teaches detecting of under-expression of NT-4 in a specific cancer, the pancreatic cancer, using an anti-NT-4 antibody, which is specific for NT-4. The art does not support the enablement of the instant claims, which encompass detecting a **genus** of numerous cancers, or tumors, including abnormal growth. Further, the antibody for NT-4 taught by the art is specific for NT-4, whereas the probe for use in the claimed method, the trkB receptor SEQ ID NO:2 or SEQ ID NO:4, is not specific for SEQ ID NO:45. The claimed probe also binds to other

target proteins BDNF and NT-3. Thus, the claimed method is **non-specific**, and not supported by the art.

3) The relative skill of those in the art

The response asserts that the relative skill in the art is high. The response asserts that in view of the high level of skill in the art, no undue amount of experimentation would be required to practice the invention since detection of labeled polypeptides is well-known and routine in the art, well within the skill level of one of ordinary skill in the art; since the specification provides detailed explanation and examples related to the claimed methods (see, e.g., pages 79-81; 86-90, particularly 86-87; and elsewhere in the application); and since it would be a matter of routine to measure over- or underexpression of a neurotrophic factor selected from the group consisting of NT-4 and NT-4/5 by measuring their binding to labeled human trkB receptor polypeptide.

The response has been considered but is not found to be persuasive for the following reasons:

The Examiner agrees that the relative skill in the art is high. However, although method of measuring the level of a protein is routine in the art, it would be undue experimentation for one of skill in the art to practice the claimed method, because of the following reasons:

1) Other than a single cancer, the pancreatic cancer, one cannot predict the level of SEQ ID NO:45 in the claimed genus of numerous cancers, as compared to that of normal, healthy individual, in view of the teaching of Soontornniyooomkij et al and Guate et al, all of record, and

2) The claimed method is non-specific, because the probe for use in the claimed method is non-specific, said probe also binds to other target proteins BDNF and NT-3, the presence of which proteins would interfere with detection of SEQ ID NO:45.

4) The unpredictability of the art

The response asserts that in that the claimed methods rely on the disclosed sequences and are also based on methods and skills that are well-known in the art. The response asserts that in addition, the application as filed explicitly discloses the pathological conditions to which the claimed diagnostic methods are directed; thus, the predictability of the art related to such diagnostic methods is quite high.

The response asserts that Soontorniniyooomkij et al. and Guate et al., directed to measurements of levels of neurotrophins and/or neurotrophin receptors, demonstrate measurements were possible and known to be of scientific and diagnostic value at the time of the invention. The response asserts that one could use such skills (as evidenced, e.g., by Soontominiyooomkij et al. and Guate et al.), to practice the invention as taught in the present application.

Concerning the non-specificity of the claimed probe, the response asserts that it is the specification that provides data for BDNF and NT-3 binding to trkB; thus, BDNF and NT-3 may bind to the trkB receptor. The response asserts that however, even if other ligands bind the human trkB receptor polypeptide, or an immunoadhesin thereof, such binding may be diagnostic of a pathological condition.

The response has been considered but is not found to be persuasive for the following reasons:

Although method of measuring the level of a protein is routine in the art, it would be undue experimentation for one of skill in the art to practice the claimed method, because of the following reasons:

1) Other than in a single specific cancer, the pancreatic cancer, one cannot predict the level of SEQ ID NO:45 in the claimed **genus of numerous cancers**, as compared to that of normal, healthy individual, in view of the teaching of Soontornniyooomkij et al and Guate et al, all of record. Soontornniyomkij et al, 1999 (Acta neuropathologica 98(4): 345-8) teach that expression of trkB proteins is characteristic of particular disease processes, as shown by the absence of BDNF and trkB protein in glia cells in AD patients, in contrast to their presence in HIV patients (abstract, last seven lines). Similarly, Guate et al, 1999 (BJU Internatl, 84: 495-502) teach that trkA and TrkC are overexpressed in prostate cancer, as compared to normal prostate tissue, while trkB is not detected in prostate cancer (abstract, p.496, second column, last paragraph).

2) The claimed method is **non-specific**, because the probe for use in the claimed method is non-specific, said probe also binds to other target proteins BDNF and NT-3, the presence of which proteins would interfere with detection of SEQ ID NO:45. Moreover, the levels of BDNF and NT-3 in a cancer are not predictable, in view of the teaching of Soontornniyooomkij et al and Guate et al, all of record, and thus they cannot predictably be used as combined with the level of SEQ ID NO:45, for diagnosis of cancer.

Moreover, one cannot predict that the truncated intracellular domain of trkB receptor, SEQ ID NO:4 (see figure 1B legend on page 3 of the instant specification), would bind to the ligand neurotrophic factor NT-4/5 (SEQ ID NO:45), in view that one cannot predict that SEQ ID NO:4 retains the binding region for the ligand SEQ ID NO:45, and in view that not any region of a receptor binds to its ligand. Thus, one cannot predict that one could successfully use **SEQ ID NO:4 for detecting the presence of SEQ ID NO:45.**

5) The breadth of the claims

The response asserts that the claims are not broad, because the methods are limited to disorders with the named characteristics, i.e. over- or underexpression of a neurotrophic factor.

The response has been considered but is not found to be persuasive for the following reasons:

The claims are broad, encompassing a method for diagnosis of numerous cancers, which either overexpress or underexpress SEQ ID NO:45, using a probe which is non-specific for the target SEQ ID NO:45.

6) The amount of direction and the absence of working example.

The response asserts that the instant application teaches how to measure levels of neurotrophins of interest in tissue using the novel trkB polypeptides of the claims.

The response has been considered but is not found to be persuasive for the following reasons:

Although the specification and the art disclose how to measure the level of the neurotrophic factor, the specification and the art do not disclose, nor have any concrete evidence of which cancer under- or over-expresses the claimed neurotrophic factor, SEQ ID NO: 45, as compared to the normal corresponding control. The specification does not have any data, or concrete evidence that the trkB receptor, SEQ ID NO: 2, SEQ ID NO:4 or an immunoadhesin thereof is a suitable, specific probe, and only detects the ligand NT-4/5 (SEQ ID NO:45).

Given the above unpredictability, and in view of the complex nature of the invention, a lack of sufficient disclosure in the specification, and little is known in the art concerning the claimed invention, it would have been undue experimentation for one of skill in the art to practice the claimed invention.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the

advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, LARRY HELMS can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MINH TAM DAVIS
February 09, 2008

/Larry R. Helms/

Supervisory Patent Examiner, Art Unit 1643